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THE DOUBLE HELIX REVISITED: A PARADOX OF SCIENCE AND A PARADIGM OF HUMAN BEHAVIOUR

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ABSTRACT

In the modern history of Science, few breakthroughs have caused an impact comparative to the Double Helix, the three-dimensional structure of DNA proposed by Watson & Crick in 1953, an event whose 50th anniversary was widely celebrated in the non-specialist media, three years ago. Although the discovery had little transcendence at the time, it has unquestionably been of great importance ever since. The Double Helix has underlined the true biological value of nucleic acids compared with proteins, demonstrating that genes are not amorphous entities but have a specific chemical composition and adopt an ordered spatial folding pattern. Elucidation of this key configuration made it possible to establish a direct relationship between the structure and the function of macromolecules, a relationship which is not so clear in the case of proteins.

During these last fifty years much has been written and argued about the circumstances surrounding the discovery and about the behaviour and attitudes of many of the protagonists. Besides Watson & Crick, other scientists, whose contribution has not been adequately recognised, played an important part in solving the Double Helix mystery. This article contains some ethical and scientific reflections which revise some of these essential contributions and throws light on the role played in history by these comparatively «*unknown soldiers*» of science. The Double Helix story is undoubtedly a manifestation of the human side of science and many scientists believe that the available evidence taken as a whole permits an alternative story to be written.

KEY WORDS: Double Helix, DNA, Watson & Crick, Wilkins, Franklin.

RESUMEN

En la desarrollo histórico de la Ciencia moderna, pocos descubrimientos han causado un impacto comparativo a las repercusiones de la Doble Hélice, la estructura tridimensional del ADN, propuesta por Watson y Crick en 1953. El 50º aniversario de aquel evento fue ampliamente celebrado hace tres años, incluso por los medios no especializados en información científica. Si bien, el descubrimiento tuvo inicialmente poca trascendencia, en este medio siglo transcurrido sus repercusiones resultan incuestionables. La Doble Hélice ha resaltado el verdadero valor biológico de los ácidos nucleicos frente a la proteínas, demostrando que los genes no son entidades amorfas. Por el contrario, poseen una composición química específica y adoptan un patrón ordenado de plegamiento espacial. La elucidación de esta configuración esencial permitió establecer una relación directa

entre la estructura y la función de las macromoléculas biológicas, dicha interconexión no resulta tan obvia en el caso de las proteínas.

A lo largo de estos cincuenta años, se ha escrito y debatido extensamente sobre las circunstancias que rodearon aquel hito, así como acerca del comportamiento y las actitudes personales de muchos de los protagonistas implicados. Además de Watson y Crick, otros científicos, cuya contribución no ha sido adecuadamente reconocida, desempeñaron un papel decisivo en la solución del misterio de la Doble Hélice. Este artículo contiene algunas reflexiones éticas y científicas que revisan esas contribuciones esenciales y pretende arrojar nueva luz sobre la participación esencial en la historia de aquellos «*soldados desconocidos*» de la Ciencia. La Doble Hélice es, indudablemente, una manifestación del lado humano de la investigación científica y muchos investigadores piensan que el conjunto de las evidencias disponibles, permite escribir una historia alternativa de la versión oficial.

PALABRAS CLAVE: Doble Hélice, DNA, Watson & Crick, Wilkins, Franklin.

INTRODUCTION

On the 25th April 1953, edition 171 of the journal *Nature* contained three articles forming part of the section entitled *Molecular Structure of nucleic acids*. The first originated in the Cavendish Laboratory, Cambridge, and was written by J. D. Watson and F.H.C. Crick¹. The second was signed, in order, by M.H.F. Wilkins, A.R. Stokes and H.R. Wilson², while the third contained correspondence of R. E. Franklin and R.G. Gosling³. The last two articles represented a culmination of the work carried out to that date by the Wheatstone Physics Laboratory of King's College, London. These no more than five, succinct pages of scientific information, described fundamental advances in the search for the structure and molecular organisation of DNA (Fig. 1), the carrier of hereditary information that Avery et al. (1944)⁴ had demonstrated nine years before, without fully appreciating the true importance of their discovery. A superficial reading of the three articles might suggest that what they described was most probably the culmination of scientific investigation carried out by three independent groups with no previous or present direct relations. The cold, rigorous and aseptic language of scientific papers in which they were

¹ WATSON, J.D. & CRICK, F.H.C. (1953), «A structure for deoxy-ribose nucleic acid», *Nature*, 171, 737.

² WILKINS, M.H.F., STOKES, A.R. & WILSON, H.R. (1953), «Molecular structure of deoxypentose nucleic acids». *Nature*, 171, 738-740

³ FRANKLIN, R.E. & GOSLING, R.G. (1953), «Molecular configuration in sodium thymonucleate». *Nature*, 171, 741-742.

⁴ AVERY, O.T., MCLEOD, C.M. & MCCARTY, M. (1944). «Studies on the chemical nature of the substance inducing transformation of pneumococcal types». *J. Exp. Med.*, 79, 137-159.

written was not capable of reflecting the arduous and tortuous path (never strewn with roses) which led to their publication.

Curiously, again nine years after the publication of number 171 of *Nature*, the full repercussions of the discoveries became manifest when, in 1962, the Nobel Prize for Physiology and Medicine was jointly awarded to Watson, Crick and Wilkins for «discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material». Scientific glory had immortalised the discovery of the Double Helix (Fig. 2), although we can only hope that the spirit of Rosalind Franklin, who had died in 1958 (when she was only 37) from ovarian cancer, was somehow present in that splendid ceremony in Sweden. Certainly her death had eased the predicament of the Swedish Academy, whose strict rules restrict the number of recipients to a maximum of three per award.

With the benefit of hindsight, it is easy to see that the official version of the «Double Helix Story» is a simplified version which, without wishing to take away one ounce of the credit due to Watson & Crick for unravelling the final knot, overlooks the important contributions made by other scientists, whose observations, experimental data and critical debate were decisive for the final step to be taken. Indeed, without their contribution, the dénouement of this scientific adventure may well have been different. In other aspects of human creativity (art, literature, the cinema, architecture, to name but a few), the result begs knowledge of the person who created it and of the influence of predecessors in its genesis. This, perhaps, is a neglected facet in scientific endeavour, since the only thing to catch the public eye is the novelty and spectacular nature of new discoveries, their potential benefits or dangers to mankind, while we lose sight of the human beings behind the same, men and women carrying their own baggage of illusions, longings, worries and -let's face it- ambitions. Like any other person on this planet of ours.

In an excellent article, A. Klug (2004)⁵ took a recent view at the series of events leading up to the discovery of the Double Helix structure of DNA. This prestigious author has always shown a keen interest in the minutiae of the subject and has had access to written documents of extraordinary value, especially the laboratory notebooks of R. Franklin which are kept in the Archives of Churchill College (Cambridge). Klug knowledgeably combines the purely scientific aspects of research with the views of the scientists concerned. From a perusal of his writings and of the abundant bibliography available, it seems clear that there exists an alternative version of the story behind the formulation

⁵ KLUG, A.(2004), «The discovery of the DNA Double Helix». *J. Mol. Biol.*, 335, 3-26.

of the Double Helix, a version that will permit us to recover the memory of great scientists unjustly overlooked during the following course of events and years. In the present article, I wish to restore the people involved to their rightful place in scientific history and to take a critical look at the way in which science is approached in society and how its results are communicated.

Throughout this contribution I shall keep in mind the opinion of the Spanish thinker Ortega y Gasset, that «Science is all that which can always be discussed»⁶ I shall not go into the exhaustive crystallographic and experimental work that led to the description of the Double Helix or the molecular organisation of DNA (Figs. 1 & 2), referring the reader instead to the magnificent analysis in this respect made by A. Klug in the above mentioned article⁷.

THE PROTAGONISTS

THE CHOSEN

James D. Watson (1928-) and Francis H.C.Crick (1916-2004)

«We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest». With this opening sentence, both prudent and daring at the same time, Watson and Crick (1953) started their immortal article «A structure for deoxyribose acid», which occupied approximately page 737 of *Nature*, as stated above⁸. The article has gone on to become considered a paradigm of scientific writing, and based on its contents, Crick & Watson were to be feted as the discoverers of the Double Helix (*Nature*, 2003)⁹. Although in the cold light of analysis, this deduction may seem correct, we consider that to fully round the circle, some of the circumstances leading to its scientific formulation should be examined again.

To the layman coming to Molecular Biology for the first time, it would seem that the discovery of the Double Helix must have been the fruit of many years of effort and dedication. However, nothing is further from the truth: Watson & Crick had never worked together, indeed did not know each other before, and their symbiotic association only began at the beginning of 1951, when, by chance or perhaps predestination, they met and began to work in the

⁶ ARGÜELLES, C. (2003), *La Doble Hélice de ADN: mito y realidad*. Murcia, Ed. Universidad de Murcia.

⁷ KLUG (2004), pp. 3-8.

⁸ WATSON & CRICK (1953), p. 737.

⁹ NATURE (Special Issue) (2003), *The Double-Helix 50 years*. 421, 395-453.

Cavendish Laboratory at Cambridge. Neither knew that this meeting was going to result in one of the most surprising and spectacular results recorded in the annals of science. Watson, a young American biologist who had gained his doctorate working in the «*phage group*», had arrived in Cambridge from Copenhagen, where he had spent an unsatisfactory post-doctoral stay under the supervision of H. Kalckar. Twelve years Watson's senior, Crick, a physicist working in crystallography with M Perutz, was still trying to complete his PhD unfortunately delayed by the Second World War, which he had spent working for the Admiralty on mine design. The discovery of the Double Helix came merely two years after these two met, and, even so, the work supporting the discovery was not of a continuous nature.

Crick & Watson carried out very little experimental work, their favourite strategy being to make molecular models out of cardboard and metal of the different components of DNA (the sugar deoxyribose, phosphates and nitrogenated bases, Adenine, Thymine, Cytosine and Guanine, or A,T,C and G) in an attempt to give these components a coherent 3-D structure. This same system had permitted L. Pauling to correctly model the folding of the α helix of proteins in strong competition with L. Bragg and M. Perutz, who were the leaders of the Cavendish Laboratory.

To construct their models with the adequate structure, precise measurements of the critical parameters were necessary, i.e. of the interatomic distances, angles of reflection and axis of symmetry. This is where both Crick & Watson gained enormous benefit from the King's College Group, particularly as regards the R. Franklin's X-ray diffraction patterns of the A (low hydration) and B (hydrated) forms of DNA fibres in solution. It must not be forgotten that Double Helix was not the first model proposed by Watson & Crick; they had previously proposed a 3-chain model with the phosphates facing inwards and the bases facing outwards. When they asked for the opinion of their colleagues at King's, it was clear from the comments made by Franklin concerning the water content that they had got it wrong. Unfortunately, Franklin's undiplomatic presumption that the two researches from Cambridge were not up to the task created a strong tension between both centres of excellence, one of the consequences of which was that Bragg decided that Watson & Crick should suspend their work on DNA. (For further reading on precise historical details, the following books are relevant: Watson, 1968¹⁰; Olby, 1974¹¹; Judson, 1996¹²).

¹⁰ WATSON, J.D. (1968), *The Double Helix*, New York, Atheneum Press.

¹¹ OLBY, R.C. (1974), *The path to the Double Helix*, London, McMillan.

¹² JUDSON, H.F. (1996), *The eighth day of creation: The makers of the revolution in Biology*, New York, Cold Spring Harbor Lab. Press.

It is far from my purpose to undermine the merits of Crick & Watson. They were rigorous, ambitious and very selective. They also learnt from their mistakes and were patient and tenacious. When they took up the challenge again, they made the following key decisions, opting for (i) a helix as the basic structure (unlike Wilkins & Franklin); (ii) a two-chain model rather than three-chain model; and (iii) the correct pairing of bases, A-T and G-C. Specially revealing is the paragraph in *Nature*, in which they foresee that the Double Helix provides the key to the universal replication of genetic material: «It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material»¹³.

THE OVERLOOKED

Twin forces propel the efforts of scientists. On the one hand, the innate, insatiable curiosity of humankind to dominate nature and to understand its mysteries, whether these mysteries are of this world or of the Universe itself. On the other hand, science is no longer the romantic pastime of the rich or dreamers, and today's scientists are professionals working for private and public institutions which hope for and, indeed, expect benefits and economic returns for their investment, if international recognition and awards accompany such returns, then so much the better.

Besides Crick & Watson, other scientists, with varying degrees of dedication, were taking part in this (the Double Helix) adventure which was to revolutionise science in the mid-twentieth century. Without doubt, they, too, deserve some of the fame and glory which history has reserved for the two protagonists. Below, we will see but a few of these names and discuss their contribution to the great event. We shall see, too, that the Double Helix game had its winners and losers, and, as always happens, there were many more of the latter.

Maurice H. F. Wilkins (1916-2004)

To include Wilkins amongst the losers might seem strange given the fact that he actually shared the Nobel Prize with Watson & Crick. However, many publications skirt round Wilkins' contribution to the discovery of the Double Helix and refer the reader to very specialised monographs if they wish to learn more. Curiously, several encyclopaedias describe him as the scientist

¹³ WATSON & CRICK (1953)

who *a posteriori* confirmed the postulates of Watson & Crick and not as the pioneer who laid the foundations of the correct spatial 3-D configuration.

Wilkins is a physicist who had spent the Second World War at Berkeley working on the analysis of uranium isotopes as part of the Manhattan Project, which would have the atom bomb as its final outcome. When the war finished, Wilkins returned to King's College, where he had trained, to work under his former director, J. Randall. There, he soon decided to abandon his research into nuclear physics and gradually turned his attention to applying physical techniques to biological processes. Long before Watson & Crick met, Wilkins had done important work on X-ray diffraction, using whole long strands of DNA in solution, based on the method developed by R. Signer in Berne (his X-ray diffraction photograph shown in Naples had so impressed Watson that he decided to ask for a transfer to Cambridge)¹⁴.

Although it is difficult to evaluate the real consequences, one unforeseen circumstance seems to have seriously affected the work being carried out at King's on the structure of DNA: the relationship between Wilkins and R. Franklin. This degenerated to such an extent that they broke off their professional relationship and Franklin transferred to Birkbeck College to work with J. Bernal. Many reasons have been put forward to explain this rupture but the most plausible being what each regarded as his/her own area of work. While Wilkins understood that Franklin had joined the group as his assistant, Franklin always considered herself as an independent researcher and acted as such. If only someone had served as mediator between the two, it is extremely possible that the story we are describing would have had a different outcome.

Rosalind E. Franklin (1920-1958)

Two factors always seem to intervene in any debate on the relevance of R. Franklin in the field of science: the fact that she was a woman and her early death in 1958 at the age of thirty-seven. Much has been written on whether she was the victim of discrimination, from paternal opposition to her scientific career to the supposed disdain of her colleagues, making of her a feminist standard bearer, a victim of the male-dominated society of her day¹⁵. Besides offering my own personal opinion, I do not have the necessary information to provide a definitive judgement on these claims, which is, anyway, beyond the scope of this article.

¹⁴ JUDSON (1996)

¹⁵ SAYRE, A. (1975), *Rosalind Franklin and DNA*, New York, Norton.

Whatever the case, Franklin's contribution to the discovery of the Double Helix is beyond doubt. It was her brilliant crystallographic work aimed at understanding the A and B structures that provided the vital clue for Crick & Watson, while the information on distances, angles and reflections which she expounded at a restricted seminar attended by Watson provided them with the support for their initial investigations.

However, Franklin's contribution was not limited to her technical ability to obtain high-resolution X-ray diffraction patterns of DNA. Even without going into great detail, she was able to reject the first model proposed by Watson & Crick, who, without her expert intervention, may well have continued along the wrong track for who knows how long. Furthermore, she was the first to propose a structure with the sugar-phosphate skeleton facing outwards and with the purine and pyrimidine bases facing inwards. The precise description of her study, which was included in the confidential report sent to the MRC sub-committee and which Perutz forwarded to Watson & Crick, was extremely useful for understanding the regularity of the C-2 symmetry.

Thanks to the detailed investigations of A. Klug (2004)¹⁶, we know that Franklin was on the way to reaching the right solution since she had noted the correct three-dimensional model in her notebook, although it is also clear that she had not realised that the two chains run in opposite directions. I truly believe that it is legitimate to raise some questions, which, unfortunately, will always remain without any definite answer. For example, why did she get misled by the «double orientation» she observed in one A form? Why did she not compare her results with those of Watson & Crick, as they had shown their work to her? And, more interestingly, would they have resolved the structure of DNA without her essential crystallographic studies? There are no obvious answers, but one thing is clear – that following the «modus operandi» of modern-day science, R. Franklin should have featured as co-author of Watson & Crick's all-important paper.

Jerry Donohue (1920-1985)

Donohue's name appears in the acknowledgements of the first article in *Nature*, where he is thanked for his contribution on certain isolated points, which were considered to be of vital importance. Nearing the end of the modelling process, Watson constructed cardboard models using the wrong base

¹⁶ KLUG (2004), pp. 8-14.

isomers since these could appear in two forms (enol and keto). Even Watson recognised that he did not know the exact formulas, which were copied from a book; he and Crick had used the enol form, whose esteric configuration did not permit the adequate conformation to establish hydrogen bonds between electronegative atoms. In fact, the first attempt proposed that each nucleotide was paired with itself (A-A, T-T, C-C and G-G), which proved unsatisfactory.

Donohue, a visiting organic chemist, shared the same office with Crick & Watson in Cambridge and, hearing the lamentations of Watson, suggested that the deficiencies might be due to the bad choice of tautomers. Without providing any proof, he suggested that the keto form would very likely be the most plausible form in nature. Strangely, his suggestion was accepted only having available some preliminary ideas from Pauling. Anyway, this Donohue's suggestion was critical and permitted the correct pairing A-T and C-G, which occupied the same spatial volumes in the structure. Again, the question arises: what would have happened without this opportune and very specific contribution of Donohue, who happened to be sharing the same office?

Erwin Chargaff (1905-2002)

Chargaff was Austrian and a brilliant biochemist attached to Columbia University. Until 1940 he had worked on methods for determining lipids and proteins, but on reading the paper of Avery et al., (1944), he clearly realised the importance of nucleic acids in Biology and he immediately switched to studying DNA. He and his group perfected chromatographic techniques for extracting and analysing the DNA from different organisms. In a revision published in *Experientia* in 1950, Chargaff concluded that the molar relation of total purines and pyrimidines and also of A and T and C and G was not far from 1, adding that «whether this is more than accidental cannot yet be said»¹⁷. Three years before Watson & Crick's model, Chargaff already had in his hand the key to explaining the configuration of DNA; it was this molecular regularity that Chargaff had glimpsed that lay behind the Double Helix.

Besides his famous «Chargaff laws», this scientist provided other important insights. In particular, he demonstrated the aperiodic nature of DNA, undermining the tetranucleotide hypothesis propounded by P. Levene, which was widely held at the time. According to this hypothesis, DNA in all living

¹⁷ CHARGAFF, E. (1950), «Chemical specificity of nucleic acids and mechanism of their enzymatic degradation». *Experientia*, 6, 201-240.

beings is organised into a repetitive and constant succession of the four nitrogenated bases. However, this monotonous language would not serve to codify biological specificity, and it was Chargaff who demonstrated that nucleotides obey no pre-established order and any number of chance configurations can occur, thus permitting individual genes to make up a specific cadence of bases that codify genetic information coherently.

Linus C. Pauling (1901-1994)

L. Pauling was without doubt one of the greatest talents in structural chemistry during the twentieth century, making fundamental contributions concerning the nature of chemical binding, electronegativity, X-ray diffraction, and many other topics in a variety of fields. His writings were compulsory (and compulsive) reading for the students of Chemistry. It was Pauling who had resolved the α helix structure of proteins as mentioned above. In this context and probably as a result of the information leaking out of England, Pauling, perhaps hurriedly and certainly erroneously, proposed a chemically wrong and unstable three-chain structure for DNA. On reading a copy of the article that Pauling's son, Peter, had received in Cambridge, Watson & Crick realised his tremendous mistake. Pauling's position in this matter has been widely debated, and there is a consensus that he was capable of correcting his error and of resolving the true conformation very quickly. However, meanwhile, he learnt from Delbruck that the definitive solution had been found¹⁸.

This slip should not be allowed to detract from Pauling's brilliant career as a pioneer in several fields besides chemistry. He propounded theories on the synthesis of antibodies, the hereditary transfer of falciform anaemia and anticipated the concept of the molecular chronometer. He was also an enthusiastic supporter of the virtues of vitamin C.

But, most importantly, Pauling merits a place of honour in history as an example of a scientist committed to the world. A convinced pacifist, he organised conferences and debates on the arms race and the dangers of nuclear war, being severely victimised in the witch-hunts of Senator McCarthy. At the height of the cold war, he was strongly criticised in the USA, and his passport was withdrawn. However, Pauling refused to give up, convening meetings of scientist opposed to weapons development, and addressing the secretary of the UN for help. He wrote a book «*No More War*», opposed the

¹⁸ ARGÜELLES (2003), pp. 90-92.

war in Vietnam and was accused of being a traitor to his country. Unusually, he was awarded two individual Nobel Prizes - for Chemistry in 1954 and for Peace on 1962¹⁹.

Oswald T. Avery (1877-1955)

Although not directly involved in the race for the Double Helix, O.T. Avery deserves to be mentioned in this commentary, if only briefly. A patient and conscientious researcher, Avery worked for more than ten years with a small group of collaborators in The Rockefeller Institute of New York, demonstrating beyond doubt that DNA is the carrier of hereditary genetic material, rather than proteins as had been previously thought²⁰. This finding published in 1944 is considered by many as the major biological discovery of the twentieth century (even of greater conceptual value than the discovery of the Double Helix). However, Avery never received the Nobel Prize for Physiology, which he well deserved, in one of the most unjust acts on the part of the scientific community against one of his own members, that can be imagined.

SOME CRITICAL REFLECTIONS ON THE DOUBLE HELIX

The above begs a series of questions and reflections, that are in no way based on scientific or bibliographic studies and which must be considered as simple opinions and conjectures of the author.

Should Watson & Crick be considered the sole discoverers of the Double Helix?

This would seem the time to ask the question which has been overshadowing all the previous pages: Would Watson & Crick have discovered the correct structure of DNA working by themselves and depending solely on their own means? In other words, are Crick and Watson the real discoverers of the Double Helix? At first sight, the answer seems obvious, since they proposed the correct model before anyone else and, therefore, the credit went to them.

¹⁹ Ibidem

²⁰ ARGÜELLES (2003), pp. 92-100.

However, the accumulation of external circumstances that favoured the development of their work, starting with previous contributions (which all scientists depend on), and consultations with a large number of specialists in other fields, who helped clarify apparently unsolvable problems, and which Watson & Crick could hardly have solved themselves, suggests that the answer to our question is not so straightforward and must be delivered with prudence.

In mathematical terms, it remains to be seen whether the final successful outcome corresponds 100% to them or whether they only deserve a fraction of the credit. Part of their success was undoubtedly due to M. Wilkins, whose contribution was recognised by his citation as joint winner with Watson & Crick of the Nobel Prize, and to R. Franklin, who unfortunately died a few years after the discovery. With no element of doubt, the crystallographic work of both scientists using DNA fibres in solution, immortalised in Franklin's unforgettable photographs of the A and B structures of DNA, was decisive in unravelling the enigma. Furthermore, other scientists too, provided information that was, quantitatively limited, but substantial as regards the clarification of confused ideas, the correction of errors and the suggestion of the accurate route to take at particular moments on the voyage towards the discovery. It is the contribution of these unsung individuals that I have tried to describe here, albeit briefly, in an attempt to adjust the historical balance. Personally, I agree with the statement that Watson & Crick were the first to publish but not necessarily to discover the Double Helix structure of DNA.

Does chance play a role in scientific research?

A famous saying, attributed to Pasteur, is that «In the field of research luck always benefits the best prepared minds». This phrase highlights the fact that the greatest scientific findings are the result of training, intelligence, effort and perseverance in the pursuit of a goal. It is therefore not pure luck or unforeseen chance (serendipity) that leads to success. A brilliant idea does not sprout spontaneously in an idle mind, nor does it occur to a layman. A strong dose of experience and the systematic application of a method known as «trial and error» is what is needed; in other words, many fruitless assays and not a few disasters may be necessary before the correct outcome comes into sight. One needs only the briefest examination of the advances made in science to see to what extent this is true.

So, does chance play no role in science? As in any other branch of human activity, chance, luck or predestination plays an important role in whether

triumph or defeat awaits an effort invested. However, in scientific research, compared with other fields where talent and creativity interact, this component must play a lesser role, especially when we think of the qualities needed by the research scientist – rigorous analysis, constancy, objectivity when proposing hypotheses and solving problems, the use of proven methods and the strict scrutiny of results. Surely, Pasteur was right: chance usually helps the best prepared because the search for truth is an active task, not a passive one, but requires a profound examination of all the nooks and crannies where it might be hiding, a continuous search for new sources and methods, the carrying out of countless experiments, many doomed to be fruitless, before a satisfactory answer is obtained.

Quite another thing from the above is the idea of «being in the right place at the right time». This is frequently applied to the case of researchers who achieve sudden fame in a field where they seem to have scant relevant experience, and when groups reach an eye-catching solution to a problem that has long escaped others. When the results of this breakthrough are published, a scientist who has made little contribution or who has only recently joined the group may be assigned an equal degree of protagonism. This does not necessarily mean that the inclusion of the newcomer's name is any way irregular or that his worth is impaired. It would be very difficult to attempt to distinguish situations of fraud and favouritism from those where a given scientist has made a valuable contribution, albeit on smaller time scale than other members of the group who have perhaps devoted years to a particular problem.

This is not mere theoretical conjecture, and should be borne in mind by young research scientists, who frequently wish (and need) to complete their training in a centre of research in a foreign country considered to be of «scientific worth». The exact nature of this research visit may well be decisive in their future scientific careers. Research laboratories are usually dynamic units, whose composition may periodically change, and, although the most important tend to be stable as regards their research staff, they do suffer their scientific ups and downs.

It is very probable that the above reflections perfectly fit the case of Watson & Crick and the Double Helix. Not doubting for a moment their natural intelligence and capacity for hard work, it is clear that fortune smiled on these two young scientists, bringing them together in the perfect setting, the Cavendish Laboratory in Cambridge, at the most opportune time -just when the crystallographic measurements of DNA made by Franklin and Wilkins had just become available. It should not be forgotten that the study of nucleic acids was not originally a priority line of research at the laboratory, and nobody was directly concerned with DNA when Watson arrived.

In King's College, on the other hand, Wilkins and Franklin were totally involved in the subject and had obtained very pure preparations of DNA in solution and had perfected the most sophisticated crystallographic methods for obtaining precise images of the X-ray pattern. These scientists had amassed a whole series of measurements when DNA was still only an object of the intellectual curiosity for Watson and Crick in their separate careers.

Do the ends justify the means in science?

If there exists such a concept as a science ethic (and many think it should), how far does it extend? As in other walks of life, we must ask ourselves if everything can be sacrificed in order to achieve success. Let's face it the search for success, or at least recognition in one's field is one the driving forces of humanity, as may be the overcoming of one's own perceived limits. In modern science, as in any supra-national activity, any advances must be recognised universally and there is tough international competition to obtain whatever funding is available to pursue these aims. As a consequence, there is enormous pressure to solve problems and quick results are the order of the day, always, of course, supported by the relevant publication (one might even say publicity). However, perhaps we should pause for one minute to wonder whether all this is not actually suffocating scientific research.

But let us return to the main story. Crick & Watson were pioneers in introducing this attitude and form of behaviour. From the outset, they wanted the equivalent of scientific immortality (not a blameworthy objective in itself). They knew it was within reach and they did not hesitate to reach out their hands to grasp it. Some details illustrate their intentions. Very shortly after embarking on their new modelling process, they proposed an obviously incorrect model, based on the following philosophy: «there is no reason why we should not know the answer quickly»²¹. In the model there were howling mistakes since they had not rigorously analysed the available data, had not correctly assembled the components and had not shown any patience. However, we must not be too strict because they were humble and wise enough to admit to having committed what today, in common parlance, would be termed a gigantic cock-up.

Now, let's look at the moments leading up to the fateful dénouement. When they had already solved the sugar-phosphate sequence in the external chain but were still stuck in the labyrinth of the bases, Wilkins suddenly sho-

²¹ WATSON (1968)

wed to Watson the famous photograph 51 depicting the B configuration of DNA without Franklin's authorisation or knowledge. Even more importantly, Watson & Crick had previously read reports on the exactitude of the atomic distance measurements through what may be termed a dubiously ethical, but certainly incorrect, procedure. Dr Randall, the director of King's College, where Wilkins and Franklin worked, had presented a research project for evaluation by the British Medical Council. The corresponding report contained detailed information of the results obtained concerning DNA. M. Perutz was a member of the evaluating committee and, basing his action on the supposed non-confidentiality of the above mentioned report, he had no hesitation in sending a copy to Watson & Crick, although there is no evidence to show that either Randall or the material authors were consulted. With this privileged information to hand, Watson & Crick were able to confirm the existence of the C-2 symmetry in the crystals. With a surprising degree of ingenuity, Watson admitted that nobody at King's had any idea of what they were doing.

One more incident is worth mentioning. When Watson understood the definitive solution provided by the famous photograph 51 and all the pieces finally fell into place, he hurriedly tried to convince the maximum authorities at the Cavendish, Perutz and Bragg, that all the evidence pointed to two chains rather than three, with a helix form repeating itself every 34 Å around the helicoidal axis. However, after the first fiasco, neither Perutz nor Bragg was willing to repeat the mistake and raised all manner of doubts and questions, while Watson felt that a once-in-lifetime opportunity was slipping away. Time was precious but Bragg, particularly, kept silent, carefully weighing up the evidence²².

It was then that Watson played his trump card, half scientific, half patriotic, by suggesting that if they did not move quickly, they would inevitably be beaten by Pauling's group from the other side of the Atlantic. Pauling was quite capable, he argued, of picking up the threads again and resolving the structure of DNA: it was just a matter of time. This was too much for Bragg and, despite his misgivings about possible friction between the Cavendish and King's, he gave permission for the new models to be constructed. Watson had known where it hurt, and had put his finger in the still open wound of a brilliant laboratory which had been defeated by American rivals (remember α helix). Another defeat at Pauling's hands would be too much to bear.

«*He who dares, wins*», and certainly there are many occasions where the more prudent or fearful lag behind and lose out as far as recognition and honours are concerned. We do not wish to question the integrity and reputa-

²² Ibidem.

tion of either Crick or Watson or imply that their success was solely due to their audacity. «Sensu strictu» they were certainly the first to propose a three dimensional structure for DNA. In many respects, their reasoning was impeccable and their ability to detect anomalies, immediately proposing more probable alternatives, was without fault. They knew what they were after and they were of the opinion that the final solution must be simple. However, it is also true that their single-mindedness and ambition to be the first, and their not totally scrupulous behaviour when it came to obtaining useful information concerning other people's data, worked in their favour.

The short-sightedness of scientists

This heading suggests another failing of research scientists. The growing professionalism and inter-group rivalry of modern day science have transformed research into a demanding pursuit that requires full-time dedication. At times scientists are so absorbed in attempting to prove the validity of their hypotheses that something very basic will escape their attention. Once a given path has been taken as true, it is very difficult to stop and consider possible alternative routes, especially when answers to the questions posed seem to be forthcoming. It is worth emphasising how often breakthroughs in science have been achieved not after a sustained research effort but as a result of giant leaps and the breaking of established taboos.

To affirm today that DNA is the substance of inheritance is a commonplace, something evident, even trivial. But all knowledge must be placed in its historical context, and sixty years ago such a statement would have seemed scientifically heretical. In those days, proteins were the main target and centre of attention in Biology. The most distinguished scientists were convinced that genes were composed of proteins. This belief was founded on good reasons, since proteins were not only structural elements of cells but seemed to possess an exclusive biological specificity: it was known that enzymes, many hormones, antibodies, membrane transporters, etc., were proteins, and so it was fair to ask why proteins shouldn't be the substance of genes.

However, when the race towards solving the structure of began in 1951, seven years had already passed since Avery et al's paper (1944)²³ had focused on the crucial importance of nucleic acids rather than proteins as a biological macromolecule. Even though a few had realised the importance of this suggestion, there was clearly a new element to be taken into account: DNA.

²³ AVERY; MCLEOD & MCCARTY (1944).

Perhaps most scientists were indeed short-sighted and did not notice that the Avery's paper implied that new directions should be taken in research. Among those afflicted were the members of the protein group at Cambridge, led by Bragg, Perutz and Kendrew, for whom it would have meant no great conceptual or methodological shift to re-direct their efforts towards examining the critical role of nucleic acids, or, at least, to have opened up a parallel line of research. However, some had understood the important changes in the air, among them Pauling, who, using his ample knowledge in structural chemistry and having beaten Cambridge in the toughly fought battle of the α helix, turned his attention to DNA²⁴.

In the research efforts, which would finish in the Double Helix, several episodes of short-sightedness occurred. A case in point is that of Chargaff, mentioned above. The surprising equimolar regularity that he had found in the proportion of the base pairs A-T and C-G held a biological secret that he was unable to decipher, despite his high level of competence²⁵.

Franklin, too, perhaps was stubborn in rejecting molecular models as a valid technique and also in recognising the fact that her brilliant photographs perfectly agreed with a helicoidal configuration for DNA. Almost certainly behind this attitude, was her true, methodical and rigorous investigating spirit, that advanced slowly by proving every hypothesis before taking the following step; she could not bring herself to put forward speculative proposals without first rigorously examining them from every angle²⁶. And neither could Wilkins, who had started the group's study in the study of DNA, find the way out of the web of crystalline fibres into the light of the final structure.

The importance of the correct approach and communication in science

A summary look at the historical circumstances surrounding many great scientific breakthroughs will show how revolutionary research almost always starts with an audacious transcendental hypothesis on the researchers' part. A fresh question, and the search for an answer by the systematic application of a scientific method is a *sine qua non* to achieve success. The nature and solidity of the work hypothesis conditions the depth and transcendence of the experimental approach taken to confirm it. As a general rule, if the question makes sense and has a solid base, fruitful results should be guaranteed. History is

²⁴ ARGUELLES (2003).

²⁵ CHARGAFF (1950).

²⁶ AVERY; MCLEOD & MCCARTY (1944).

full of well-prepared scientists, who, with suitable means at their disposal, have failed to answer questions that were wrongly formulated or mere chimeras. Although not unheard of, it is extremely unusual for ill-based ideas to provide truthful information, although they may be useful for detecting important conceptual errors, so that the investigator understands his or her mistakes and can redefine a proposal in valid terms.

On the other hand, the correct hypothesis is not necessarily orthodox. Indeed, most great conceptual leaps have implied a sharp break from the scientific doctrine of the day. Crucial discoveries have been made by free-thinking scientists who had the clarity of mind to ask a question that went against the beliefs held at the time. Such «*madmen*» were frequently discredited, if not mocked, by their contemporaries and only time and the light of scientific rigour have revealed the truth of their proposals and have led to the rediscovery of their work. Many did not live long enough to see their theories proved and to receive the acknowledgement they were due²⁷.

In this context, Watson & Crick may be considered a paradigm. From the beginning, they had the helix configuration in their minds and they predicted some scientific conclusions in this light. Despite their first unsuccessful attempt, they were able, with the invaluable help of colleagues, to rectify and critically analyse the data, correctly deducing the specific pairing of the purines and pyrimidines bases, the significance of the C-2 symmetry and the anti-parallel orientation of the strands. Finally, their insistence on constructing molecular models was seen to be the most appropriate for the task at hand, permitting them to finally fit all the pieces together and thus obtain the Double Helix. The importance of their attitude must be stressed, and they always had the final goal in their minds. Perhaps their way of working was not strictly rigorous or even scrupulous but they were certainly an astute pair, discriminating the essential information from the accessory, correctly diagnosing their mistakes and not «*barking up the wrong tree*» when it was obviously not the correct one.

Finally, let us look at the importance of communication in the diffusion of scientific discoveries, both for any immediate public repercussion and for the subsequent recognition of the authors. Many scientists have conjectured that if Watson & Crick had not hit the right note in anticipating the precise structure of DNA, it would have been discovered in two to three years, anyway. The same scientists also speculate that if the discovery had not been commu-

²⁷ ARGÜELLES, J.C. (2001), «The corollary of scientific research: "Publish or be damned"». *Internatl. Microbiol.*, 3, 193-194.

nicated in its entirety as a brilliant *coup de théâtre* that surprised everyone, the mystery would have been revealed gradually through the slow release of partial data, the impact would have been considerably less. Indeed, the articles of Wilkins, Franklin and their collaborators which were published in the same number of *Nature* following Watson & Crick's article, contained a greater mass of data and scientifically more consistent information, but did not have anything like the same impact.

CONCLUDING REMARKS

A thorough study of the long road leading to the discovery of the Double Helix, with all its twists and turns, is an obvious example of «*the human side of scientific research*», an element sometimes overlooked or, at least, undervalued by public opinion.

But the Double Helix story also represents a invaluable insight into doing, living and sharing science that is a relic of a bygone age. In those days, concepts such as the «impact index», «competitiveness», «number of citations» were unknown. *Science for science's sake* might have been the motto of researchers. Scientific research groups were small and primarily concerned with the advance of knowledge, to which end they worked slowly and steadily. Half a century later, this *modus operandi* has been replaced by «*assembly line science*» in factories of scientific production. Rather than investigate in the true sense, efforts are directed at obtaining quick results, which will unlock access to the ever-diminishing funds available for scientific research.

In those days, calm reflection and discussion were important before writing a scientific paper. It was not necessary for a reputed scientist to publish a pile of papers to become respected, to retain that respect, and to obtain sufficient funding. Great value was placed on specialist seminars, where scientists would submit their work to the critical appraisal of their colleagues in the form of a report (not yet published) on their latest findings. In such meetings, information would be shared without fear that others would «*borrow*» ideas and publish first. In some way, this way of doing things was overturned by Crick & Watson's strategy, as they attempted to resolve the Double Helix.

It is not surprising, given its transcendental importance, that DNA should turn out to be a molecule with a much simpler design than that of proteins and that its self-replicating function would be obvious merely from an inspection of its configuration. Whereas the form of the Double Helix immediately suggests a DNA copying mechanism, the same cannot be said of the information available upon analysing the primary sequences of proteins. It was Crick who

attributed this structural divergence between nucleic acids and proteins to the singular nature and biological mission of nucleic acids.

It would be difficult for such a discovery to be made today. Crick was right again when he claimed star status for this singular structure. Besides being an intrinsically beautiful macromolecule, it has its own internal logic as carrier of *the secret of life*, and is capable of satisfying two basic requirements: the ability to make exact replicas of it self and to transmit a reliable code of instructions for the construction of a new being. Such a simple model as that offered by nature, logical and elegant at the same time, could never have occurred to any inventor charged with designing this molecular configuration. Watson himself stated that the Double Helix was far too beautiful a structure for it not to be true.

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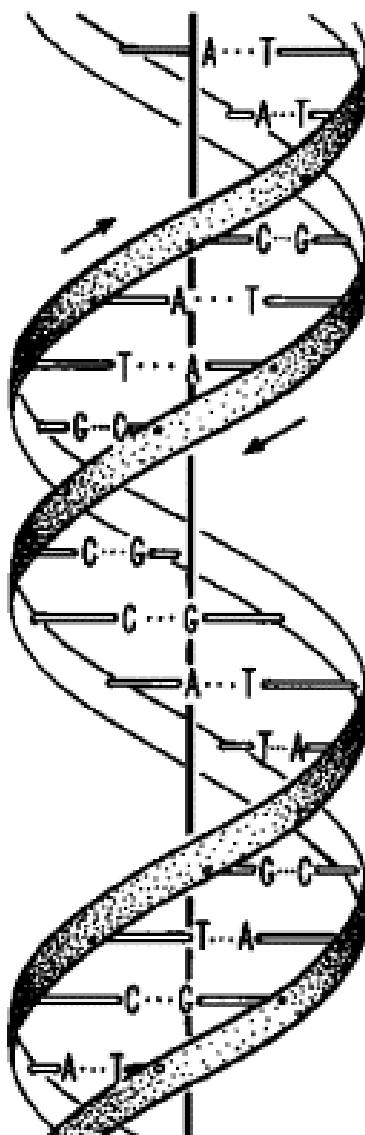


FIGURE 1. Schematic representation of DNA, following the general sketch of the Double Helix. The sugar (2-deoxyribose)-phosphate group makes up the backbone, whereas the side groups consist of purine (adenine and guanosine) or pyrimidine (cytosine and thymine) bases. The two chains run in opposite directions. This schematic illustration matches the original proposal by Watson & Crick (1953)

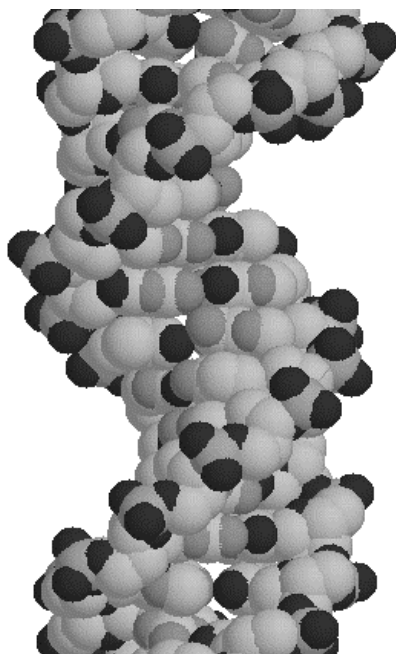


FIGURE 2. A three-dimensional atomic model of DNA, constructed according to the rules of the Double Helix. Avery et al. demonstrated that DNA was the chemical substance of genes, harbouring the transmissible hereditary information.